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The Role of Environmental Factors in the Etiology of Non-syndromic Orofacial Clefts in the Ethiopian Population

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Abstract

Background: Non-syndromic orofacial clefts (NSOFCs) represent the most common congenital anomalies in the head and neck region. Multiple factors contribute to the occurrence of this anomaly. The etiology of NSOFCs in the Ethiopian population has not been investigated prior to this study.

Aims of the study: To assess the role of maternal environmental factors in the occurrence of NSOFCs in the Ethiopian Population.

Methods: We used unmatched case control study design and evaluated the role of environmental factors to the occurrence of NSOFCs in the Ethiopian population. The participants were recruited from the same institution (Yekatit 12 Hospital Medical College). We studied 760 mothers (359 mothers of children born with NSOFCs and 401 mothers of children born without any congenital anomalies). Univariate and multivariate logistic regression analyses were used to calculate relative risk by odds ratio (OR) and 95% confidence interval.

Results: Mothers who gave history of bronchial asthma and mothers who were admitted for threatened abortion had a higher risk of delivering a child with NSOFCS p-value=0.013; AOR=**0.194, 95% CI [0.053-0.712],** p-value <0.001; AOR= **0.179, 95% CI [0.091-0.352]** respectively. Higher number of children with NSOFCs were born to mothers who were exposed to diagnostic X-ray investigation during early pregnancy than those who were not exposed p-value 0.048; AOR=**0.375, 95% CI [0.142-0.990].**

Conclusion: Maternal exposure to diagnostic x-ray, maternal chronic illness like bronchial asthma and threatened abortion were found to be associated with the occurrence of NSOFCS in the studied population.

Key words: Non-Syndromic Clefting, etiology, maternal factors

Introduction

Orofacial Clefts (OFCs) are major congenital defects with a worldwide prevalence of 1/700 live births [1],[2]. The incidence of this anomaly in Africa varies from 0.44/1000 live births to 1.65/1000 births [3],[4]. The incidence of this anomaly in Ethiopia is 0.44/1000 live births [3] while in Addis Ababa it is 1.49/1000 live births [5].

At the moment OFCs are not major cause of mortality in developed countries but cause considerable morbidity. The effect on affected children goes beyond the noticeable defect of face and extends to repeated infections, social stigma, and mental impairment. It can also affect the speech, hearing, and teeth formation[6].

OFCs can be described as part of a syndrome where it is called syndromic and Non-syndromic or isolated when it occurs without other malformations or syndromes. The syndromic forms present with other congenital anomalies. Non-syndromic clefts are said to be multi factorial in origin. Genetic predisposition and various environmental factors can contribute to the occurrence of Non-Syndromic Orofacial Clefts (NSOFCs) especially if they act at the relevant time of embryologic development. The contribution of environmental factors is high in genetically predisposed patients [1]. These include alcohol consumption [7], maternal illness and smoking [8]. A study done by Puho et al in Hungary found out that [9] mothers who were treated with, phenytoin, oxprenolol, thiethylperazine and amoxicillin during the first trimester of pregnancy had an increased risk of delivering a child with CL/P.

The etiology of this common anomaly is not known in Ethiopia. Investigating the contribution of factors such as socioeconomic status and exposure to environmental factors in relation to the occurrence of NSOFCs in different populations at different locations may contribute in the identification of factors associated with NSOFCs. Therefore, the aim of this study was to assess the role of maternal factors which included maternal demographic data, maternal exposure and maternal illness in the occurrence of NSOFCs in the Ethiopian population.

Methods

Study area and setting

The study site was Yekatit 12 Hospital Medical College reconstructive surgery unit and pediatrics department of the same hospital in Addis Ababa, Ethiopia. Yekatit 12 Hospital is one of the oldest public hospitals, which provide general and tertiary level service for all the disciplines. The cleft center at this hospital is the only center in Ethiopia that provides multidisciplinary cleft care for patients born with OFCs. This center was established with the support of the Bergen Cleft Team, Norway sponsored by Norad in 2003. It is now providing the care in collaboration with charity organizations (Transforming Faces and Smile Train). The pediatrics department at this hospital is a teaching center; it is affiliated to Addis Ababa University College of Health Sciences School of Medicine. In this department is one of the few neonatology units in the country, it receives patients from all parts of Ethiopia. The payment to see a doctor at this unit is minimal and if the family cannot afford to pay this minimal payment they will receive a free treatment but they will be asked to bring a paper from their locality which confirms that they are poor and cannot afford to pay for the treatment of their child or their own. The data collection period ranged from November 1, 2012 to January 30, 2016. The children (cases and controls) age ranged from few days two four years. More than 50% of the children age was less than six months and more than 75% was less than 1 year old.

Study design

We used unmatched case control study design to determine the contribution of maternal demographic data, maternal medication use, maternal illness, maternal life style and exposure to the occurrence of NSOFCs in the Ethiopian population. Both case and control mothers were interviewed by trained research assistants using study questionnaire adopted from the NaigeriaCRAN study [10]. We interviewed 760 mothers, who were divided into 2 groups: 359 mothers of children born with NSOFCs (cleft lip only 140, 39.0%, Cleft Lip and Palate 187, 52.0% and Cleft Palate only 32, 9.0%) and 401 control mothers (mothers of children born without any congenital anomaly). We obtained information on maternal medical history, lifestyle, exposure, etc. in the peri-conception period and first trimester of pregnancy. In the majority of the participants (75%)

information was collected within the first year of child birth. The data were collected from November 2012 to January 2016. We have excluded from the analysis mothers who gave history of clefts in their first and second degree relatives (CL/P 16, CPO 3) and also excluded mothers who delivered a child with syndromic cleft lip and or palate all together 10, one of the mothers delivered a child with Van Der Woude syndrome, another with pierre robin sequence, the other two mothers delivered children with Tessier 1 and 13. The remaining syndromes were unknown. The child who was born with Van Der Woude syndrome had bilateral complete cleft lip and bilateral lower lip pits. She was included in our previous publication [11].

Inclusion Criteria: Mothers of children born with NSOFCs who visited our unit and who agreed to participate included. The controls were also from the same hospital that brought their child for treatment other than congenital anomaly of any type

Exclusion Criteria: Mothers of children born with syndromic clefts and Mothers who gave history of cleft in their first and second degree relatives'.

Data Collection

The questionnaire used for the NigeriaCRAN [10] study was adapted, modified and used for this study. The trained research assistants, principal investigator and collaborators interviewed the participants. The parents of the index child approached and invited to take part in the study. The details obtained from each family were mothers' demographic data such as (maternal age at delivery, gestational age; educational level); folic acid intake, vitamin supplementation, other medications use, maternal illness, maternal tobacco use, and alcohol consumption during the peri-conception and first trimester of pregnancy. In addition, information on the delivery status and birth weight of the index child was obtained.

Data analysis and statistics

In order to assess the role of environmental factors in the occurrence of NSOFCs in the Ethiopian population we collected data using questionnaire. The collected data were entered into an excel worksheet, cleaned and transferred to SPSS version 20 for analysis.

Descriptive summaries such as frequencies, percentages and proportions were determined and presented in tables. To identify variables which contribute to the occurrence of NSOFCs first binary logistic regression analyses was carried out and candidate variables for multivariable model at p-value <0.05 were determined. We then identified the factors significantly associated with the risk of NSOFC occurrence by entering variables that were associated with the occurrence of NSOFCs in the binary logistic models at P-value<0.05 in the multivariate logistic regression model. First descriptive data were presented in tables and association between maternal factors and the occurrence of NSOFCs was determined by calculating odds ratio (OR) and 95% confidence interval (CI).

Ethical consideration

The research protocol was reviewed and approved by IRB College of Health Sciences, Addis Ababa University No: 042/2012; Protocol No: 00/10/Surg and by NRERC 3.10/715/04 EC after that yearly renewed. We also retrieved informed consent from the participants.

Results

We included 760 mothers in this study: 359 mothers of children born with NSOFCs (cleft lip only n= 140, 39.0%, Cleft lip and palate n=187, 52.0% and Cleft palate only n= 32, 9.0%) and 401 mothers of children born without any identifiable birth defect). The demographic data of the participants like mother's age at the birth of the index child, educational level, location during pregnancy etc. are presented in Table 1.

The majority of the mothers in this study lived in Addis Ababa (n=350, 46.1%) during their pregnancy followed by Oromia (n=173, 22.8%) (Table1). Mothers who lived in other regions during their pregnancy had a higher risk of delivering a child with NSOFCs than those mothers who lived in Addis Ababa (reference category) Table 1. We observed that NSOFC was more common in macrocosmic children and in children with low, very low birth weight and in those whose birth weight was not known, when it was compared with children born with normal birth weight reference group Table 1

We assessed the role of maternal smoking, alcohol consumption and exposure to diagnostic x-ray during the first trimester of pregnancy and found out that exposure to diagnostic x-ray was a risk factor p-value 0.011, COR **0.318,** 95% CI **0.132-0.765.** Table 2.

We also assessed the role of maternal illness and maternal medication use with the occurrence of NSOFCs in the offspring and found out that mothers who suffer from Bronchial Asthma, threatened abortion and mothers who suffered from severe vomiting (hyperemesis gravidarum) were at a higher risk of delivering a child with NSOFCs with p-value 0.022; COR 0.268; 95% CI 0.087-0.830, p-value <0.001, COR 0.290; 95% CI 0.161-0.523 and p-value 0.031;COR 1.479; 95% CI 1.036-2.111 respectively. Table 3. All mothers who suffer from bronchial asthma reported to use some bronchodilators. The association of maternal folic acid, iron and other medication use with the occurrence of NSOFCs was assessed but no significant association was found Table 3.

Binary logistic regression analysis showed that maternal residential area, socioeconomic status indirectly shown by (maternal education, number of previous births and number of unattended delivery), maternal exposure to diagnostic X-ray, maternal illness (bronchial asthma, vomiting and threatened abortion) were associated with the occurrence of NSOFCs. Tables: 1, 2 and 3. The number of previous birth and unattended delivery (unknown birth weight) was used as an indicator of the socioeconomic status because if a family is well to do and educated they have a better chance and understanding to attend family planning services. Some variables like maternal education, number of previous births and maternal illness (vomiting) were significantly associated with the occurrence of NSOFCs. However, the association was not persistent in the multivariate model when it was adjusted for other variables Table 4.

There was no difference between the case mothers and control mothers with regard to the use of folic acid, iron and other medications before and during first trimester of pregnancy. Very few mothers of both groups reported to take folic acid and other vitamins before and during first trimester of pregnancy. The use of folic acid and iron was found to be more common during the second and third trimester of pregnancy in both groups.

Discussion

The contribution of maternal environmental factors to the occurrence of non-syndromic orofacial clefts in the Ethiopian population was assessed using unmatched case control study design. We collected data from 760 mothers: 359 mothers of children born with NSOFCs and 401 mothers of children born without any congenital anomaly. We evaluated the role of exposures like smoking, alcohol consumption and exposure to diagnostic X-ray during first trimester of pregnancy.

We showed that mothers who had exposure to diagnostic X-ray during first trimester of pregnancy had a higher risk of delivering a child with NSOFCs. Similar to our study Mohammad Zandi et al[12] found significant association between maternal exposure to diagnostic X-ray during pregnancy and the occurrence of NSOFCs in the offspring. Sutapa Bandyopadhyay Neogi et al [13] in an Indian study found significant association between the occurrence of OFCs and diagnostic X-ray exposure in the first three months of pregnancy.

In our study maternal smoking was not found to be a risk factor for delivering a child with NSOFCs. This is in contradiction to the findings of other researches done in different part of the world. Kallen [14] did a case-control analysis in Sweden and found significant association between maternal smoking and non-syndromic cleft lip and or palate in the offspring. In a meta-analysis using 11 published studies Wyszynski *et al [15]* found significant association between maternal smoking and NSOFCs. The role of passive smoking in the etiology of OFCs clefts was evaluated and found to be significantly associated [16]. An increased risk of non-syndromic cleft lip and or palate in the offspring of smoking mothers in the Danish and Iowan case control studies was observed by Min Shi et al [17]. Asghar Ebadifar et al [18] found significant association between maternal smoking and increased risk for oral clefts. Even though the prevalence of smoking reported among the mothers of children born with orofacial clefts (7%) was higher than the overall prevalence of tobacco uses in the country (4.1%) reported by lakew and Haile [19] it is not different from the smoking prevalence reported among the

control mothers. The lack of association might be related to the small number of mothers reported to smoke.

This study also evaluated the relationship between maternal vomiting and threatened abortion during first trimester of pregnancy and the occurrence of NSOFCS and found out that threatened abortion was significantly associated. We also showed that low socioeconomic status indirectly indicated by the high proportion of an attended delivery (unknown birthweight), multiple births and low maternal education were associated with the occurrence of NSOFCs. This is similar to Kraples et al [20] and N Taghavi et al [21] studies. Kraples et al. speculated that low socioeconomic status can be a marker of parental health and life style therefore should be considered as a risk factor. Warkany et al associated nutritional deficiencies with cleft palate in animal studies [22]. Education plays a role in changing the life of individuals. The chance of getting healthy diets and nutrients for uneducated individuals is less. Maternal healthy diets and nutrients are very important for the normal development of a fetus. Nutritional deficiency in mothers before conception and during early pregnancy could lead to failure of cell growth, differentiation, migration and fusion. This alone or in combination with other factors could cause orofacial clefts.

We assessed the impact of using folic acid, vitamins and other medications on the occurrence of NSOFCs but found no association, this could be because very few mothers reported that they took vitamins and other medications. Butali et al [23] in an individual participant data (IPD) meta-analysis found reduced risk of CL(P) with maternal folic acid use. Ce´cile Chevrier et al [24] assessed the role of folate intake and the risk of Non-syndromic oral clefts and detected that control mothers had a significantly higher average dietary folate intake than case mothers.

Strength and limitations

The study site for this study was Yekatit 12 Hospital Medical College Cleft Lip and Palate center, which is the only cleft center in the country, which provides holistic cleft care. Because of this we receive patients from all parts of the country. This and the large sample size enabled us to extend the results to the Ethiopian population. We also evaluated the contribution of the main exposure factors, which were evaluated in other

studies. The main limitation of this study was that environmental exposure data was collected retrospectively leaving room for recall bias. The other limitation was the study did not include cases which occurred in still births, in termination of pregnancy and those who died young before referral to the study institution for treatment. We analyzed all NSOFCs combined not separately by phenotypes this could be another limitation.

Conclusion and Recommendations

In conclusion, this study for the first time demonstrated the association of some maternal environmental factors in the etiology of NSOFCs in the Ethiopian population. We observed significant association between exposure to diagnostic X-ray and the occurrence of NSOFCs. A statistically significant association between maternal illness (threatened abortion, bronchial asthma) and the occurrence of NSOFCs was observed. We also observed that very few case and control mothers took folic acid and other vitamins before and during first trimester of pregnancy. Preventative public health measures can decrease some of the congenital anomalies. We recommend preventative health care measures, which include improving the diet of women throughout their reproductive years, ensuring an adequate dietary intake of vitamins and minerals, and particularly folic acid, through daily oral supplements or fortification of staple foods such as wheat or maize flours

Any exposure of pregnant women to medications or medical radiation e.g. imaging rays should be justified, based on careful health risk–benefit analysis. The education of health care professionals and others involved in promoting prevention of congenital anomalies should be strengthened.

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